DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

m33224

December 23, 1999

CBER-00-010

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Antonio Boniolo
Business Leader, Diasorin Europe
Diasorin s.r.l.
Via Crescentino
13040 Saluggia, Italy

Dear Mr. Boniolo:

The Food and Drug Administration (FDA or the agency) conducted an inspection October 18 through 25, 1999 of your facility located at Via Crescentino, Saluggia, Italy. During the inspection, FDA investigators documented violations of Section 501(h) of the Federal Food, Drug, and Cosmetic Act and deviations from the applicable standards and requirements of Title 21, Code of Federal Regulations, (CFR) Subchapter H, Part 820, as follows:

1. Failure to investigate the cause of nonconformities related to product, processes, and the quality system [21 CFR 820.100(a)(2)]. For example:

   a. the replicate ——— residual moisture test results for Reagent A lot # 3290620 were 3.4%, 4.9%, and 3.9%. The 4.9% result exceeded the release specification of ——— A non-conformance was not issued and an investigation was not conducted.

   b. the ——— residual moisture test record for Reagent B lot # 3280620 had results of 10.4%, 1.2%, 0.3%, 0.6%, and 1.0%. The 10.4% result was changed to 1.4% by the analyst and discarded. The 0.3% and 0.6% results were added together and averaged with the 1.2% result. The final result was 1.2% and the test record was approved. There were no explanations or investigations of the test discrepancies.

c. [redacted] Lot #10 failed a sterility test on 01/28/99. There is no investigation or non-conformance record for the sterility failure.

2. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications [21 CFR 820.70(a)]. For example:

   a. test practices are inconsistent in that quality control Standard Operating Procedure (SOP) CB323, entitled [redacted] requires testing [redacted] replicates for the [redacted] method and the production SOPs, MFSP1 (Reagent B) and MFCN5 (Reagent A), require the testing of [redacted] replicates for the [redacted] method.

   b. SOP CB213, entitled [redacted] requires a [redacted] There are no records that this control is performed.

   c. SOP 10.0004, entitled [redacted] does not include media fill procedures to simulate loading, processing and unloading of the lyophilizer, procedures for capping, filling process interruptions, and environmental monitoring.

   d. there is no evidence that periodic growth promotion testing of prepared media with [redacted] expiration dates has been performed as required in SOP 10.0004, entitled [redacted]

   e. preservative effectiveness studies have not been performed for the following products and their components: AB-AUK-3, AUK-3, AB-COREK, ETI-AB-COREK, and [redacted]

3. Failure to establish and maintain procedures to prevent contamination of equipment or product substances that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(e)]. For example:

   a. mold was observed on the walls and ceiling of walk-in cooler [redacted] In addition, a majority of the flooring in the approximately [redacted] cooler was covered in carpeting.

   b. bacteriostatic and fungistatic properties of U.S. licensed products have not be assessed to determine their effects on sterility testing.

4. Failure to establish and maintain procedures for the use and removal of manufacturing material to ensure that it is removed or limited to an amount that does not adversely affect the device's quality [21 CFR 820.70(h)]. For example:

   a. cleaning validation studies have not been performed on chromatographic columns used for protein purification.

b. the January 1998 cleaning validation for the ——— plate coating filling heads is incomplete in that the dates of the procedures and the personnel who performed them are missing. In addition, there is no documentation that cleaning procedures were followed.

5. Failure to establish and maintain procedures for process validation in order to ensure that processes have been adequately validated and that the specified requirements continue to be met [21 CFR 820.75] in that the lyophilization process for the ——— ———————————— have not been validated.

6. Failure to establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained [21 CFR 820.72].

a. the last calibration of measurement equipment in the lyophilizer was in 1995.

b. there is no evidence of —— calibration of the pH meter located in Bulk Preparation Room #7 as required in SOP 09.0110, entitled ———— ———

7. Failure to establish and maintain procedures to adequately control environmental conditions that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(e)] in that there is no validation data to establish surface sampling sites and surface sampling frequency

8. Failure to ensure that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use [21 CFR 820.70(g)] in that the Gamma Counter Data Transfer Validation, dated March 31, 1999, did not include installation/operation qualification results and a worst case challenge.

9. Failure to maintain specifications as part of the Device Master Record [21 CFR 820.181] in that SOP CQcce203 entitled, ———————————————— — does not include a specification for the maximum number of adjustments that can be made without an investigation.

We acknowledge receipt of your written response dated November 18, 1999, to the Form FDA-483 issued at the close of the inspection. We have reviewed your response and find that it is inadequate to address our concerns and have the following specific comments to your response, which are numbered to correspond to the observations listed on the Form FDA-483:

1a. Please clarify if the revised SOPs will address whether individual out-of-specification test results will be investigated when test data averaging techniques are used.

8, 9. Please clarify whether the revised SOPs will include filter integrity testing.

10. Please indicate what actions will be taken in reference to the carpeting in the walk-in cooler ———

11. Please indicate whether validation data will be used when choosing sampling points.

15a. Please clarify your statement that "the out-of-specification results observed were due to miscalculation and not to erroneous results."

20. Please provide the maximum number or percentage of adjustments that will be made without an investigation. Include the statistical rationale used to establish these limits.

Neither the above violations nor the observations noted on the Form FDA 483, presented to you at the conclusion of the inspection, are intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility to ensure adherence to each requirement of the Federal Food, Drug, and Cosmetic Act and the applicable regulations and standards. The specific violations noted in this letter and on the Form FDA 483 may be symptomatic of serious underlying problems in your establishment's manufacturing and quality systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

You should take prompt action to correct these deviations. Failure to do so may result in regulatory action without further notice. Such action includes license suspension and/or revocation, and/or import alert, which would prevent your product from entering the United States. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts. In addition, no license applications or supplements for devices to which the deficiencies are reasonably related will be approved until the violations have been corrected.

You should respond to FDA in writing within 15 working days of receipt of this letter of the steps you have taken to correct the noted violations and to prevent their recurrence. Corrective actions addressed in your previous letter may be referenced in response to this letter, as appropriate. If corrective actions cannot be completed within 15 days, state the reason for the delay and the time within which the corrections will be completed. FDA will verify your implementation of the promised corrective actions during the next inspection of your facility.

Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610. If you have any questions regarding this letter, please contact Cathy Conn at (301) 827-6201.

Sincerely,

Deborah Ralston
Director
Office of Regional Operations